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Chapter 64: Glaucoma

INTRODUCTION

- *Glaucomas* are ocular disorders that lead to an optic neuropathy characterized by changes in the optic nerve head (optic disc) associated with loss of visual sensitivity and field.
- There are two major types of glaucoma: *primary open-angle glaucoma* (POAG) or ocular hypertension, which accounts for most cases and is therefore the focus of this chapter, and *primary angle closure glaucoma* (PACG). Either type can be a primary inherited disorder, congenital, or secondary to disease, trauma, or drugs.
- Intraocular pressure (IOP) is a poor predictor of visual field loss; however, the risk of visual field loss increases with increasing IOP. IOP is not constant; it changes with pulse, blood pressure, forced expiration or coughing, neck compression, and posture. IOP demonstrates diurnal variation with a minimum pressure around 6 PM and a maximum pressure upon awakening.
- The balance between the inflow and outflow of aqueous humor determines IOP. Pharmacologic studies suggest that α_2-adrenergic agonists, β-adrenergic blockers, dopamine blockers, carbonic anhydrase inhibitors (CAIs), melatonin-1 agonists, and adenylate cyclase stimulators decrease aqueous inflow by reducing aqueous humor production. Outflow is increased by cholinergic agents (eg, pilocarpine), which contract the ciliary muscle and open the trabecular meshwork, and by prostaglandin analogs and α_2-adrenergic agonists, which increase uveoscleral outflow.
- Many medications can increase IOP (**Table 64-1**). The potential to induce or worsen glaucoma depends on the type of glaucoma and on how well it is controlled.

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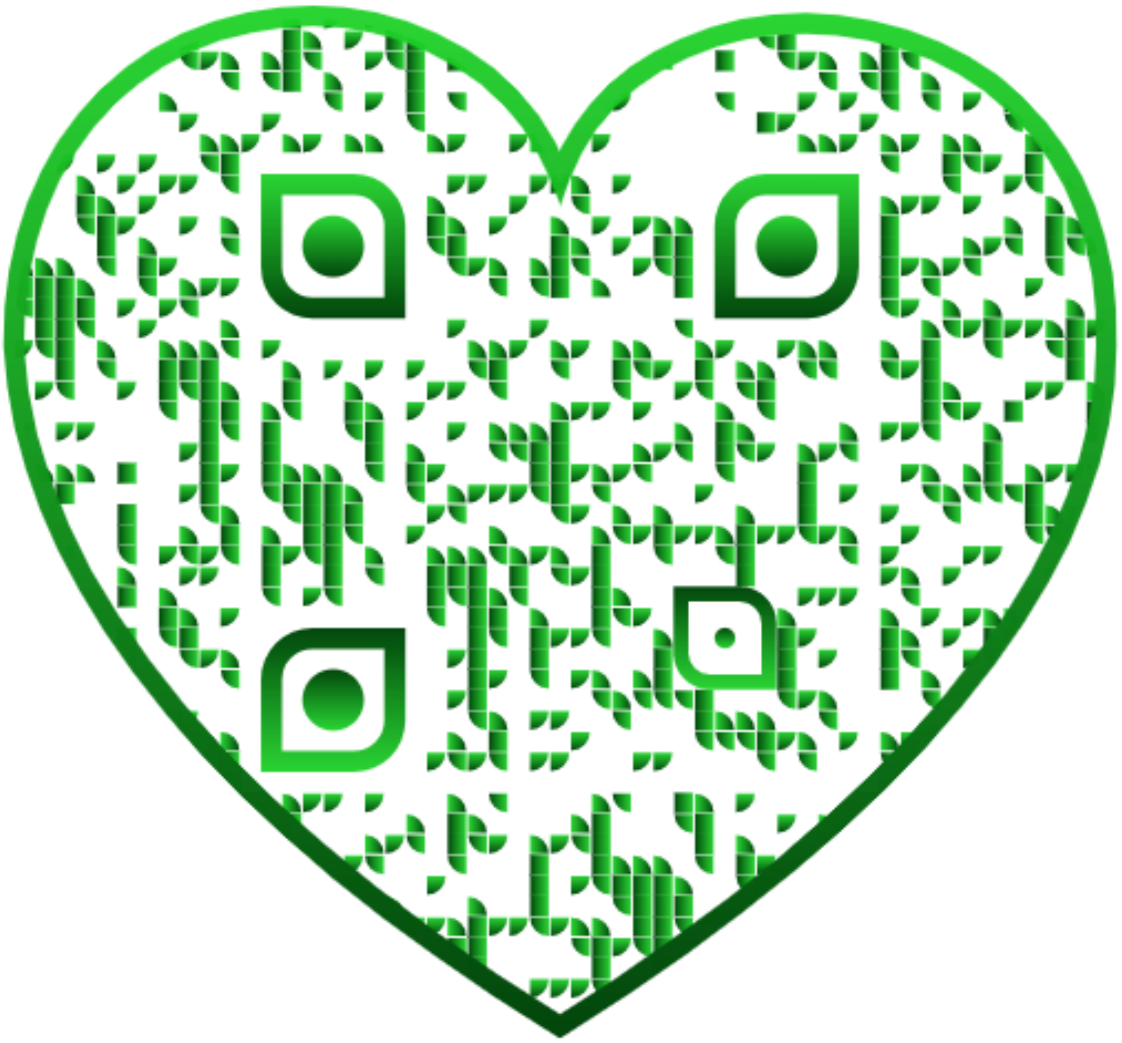

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TABLE 64-1

Drugs That May Induce or Potentiate Increased Intraocular Pressure

Open-Angle Glaucoma
Ophthalmic corticosteroids (high risk)
Systemic corticosteroids
Nasal/inhaled corticosteroids
Fenoldopam
Ophthalmic anticholinergics
Succinylcholine
Vasodilators (low risk)
Cimetidine (low risk)
Closed-Angle Glaucoma
Topical anticholinergics
Topical sympathomimetics
Systemic anticholinergics
Heterocyclic antidepressants
Low-potency phenothiazines
Antihistamines
Ipratropium
Sumatriptan
Topiramate
Duloxetine
Lactulose (low risk)
Metoclopramide (low risk)
Benzodiazepines
Daratumumab
Theophylline (low risk)
Vasodilators (low risk)
Systemic sympathomimetics (low risk)
Central nervous system stimulants (low risk)
Serotonin-selective reuptake inhibitors
Imipramine
Venlafaxine
Tetracyclines (low risk)
Carbonic anhydrase inhibitors (low risk)
Monoamine oxidase inhibitors (low risk)
Topical cholinergics (low risk)

CLINICAL PRESENTATION

- POAG is a bilateral, often asymmetric, genetically determined disorder constituting 60%–70% of all glaucomas and 90%–95% of primary glaucomas in the United States. It progresses slowly and is usually asymptomatic until the onset of substantial visual field loss. Central visual acuity is maintained, even in the late stages.

- Patients with PACG typically experience intermittent prodromal symptoms (eg, blurred or hazy vision with halos around lights and, occasionally,

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headache). Acute episodes produce symptoms associated with a cloudy, edematous cornea; ocular pain; nausea, vomiting, and abdominal pain; and diaphoresis.

DIAGNOSIS

- POAG is confirmed by the presence of characteristic optic disc changes and visual field loss, with or without increased IOP. *Normal tension glaucoma* refers to disc changes, visual field loss, and IOP less than 21 mm Hg (2.8 kPa). *Ocular hypertension* refers to IOP greater than 21 mm Hg (2.8 kPa) without disc changes or visual field loss.
- IOP is generally markedly elevated (eg, 40–90 mm Hg [5.3–12 kPa]) in PACG when symptoms are present. Additional signs include hyperemic conjunctiva, cloudy cornea, shallow anterior chamber, and, occasionally, edematous and hyperemic optic disc.

TREATMENT OF OCULAR HYPERTENSION AND OPEN-ANGLE GLAUCOMA

- Goal of Treatment: To lower the IOP to a level associated with a decreased risk of optic nerve damage, usually a 25%–30% decrease from baseline.
- Initiate drug therapy in a stepwise manner (**Fig. 64-1**), starting with lower concentrations of a single well-tolerated topical agent (**Table 64-2**). Therapy can be started in one eye (except for patients with very high IOP or advanced visual field loss) to evaluate drug efficacy and tolerance.
- Topical β-blockers (eg, **timolol**, **levobunolol**, **metipranolol**, **carteolol**, **betaxolol**) are first-line agents with a long history of successful use, providing a combination of clinical efficacy and general tolerability. Prostaglandin analogs (eg, **latanoprost, bimatoprost, travoprost, tafluprost)** are also used as first-line therapy; they offer once-daily dosing, better IOP reduction and control over 24 hours, good tolerance, and availability of lower-cost generics. **Latanoprostene bunod** is a prodrug of latanoprost and is also metabolized to a nitric oxide–donating moiety, providing dual mechanisms for increasing aqueous outflow. **Brimonidine** and topical CAIs are well-tolerated and effective agents for second-line therapy.
- If more than one agent is needed, fixed combination products reduce the number of daily doses, which might improve adherence and prevent washout effect seen when a second medication is administered too soon after the initial medication. They also reduce exposure to ophthalmic preservatives.
- **Pilocarpine** is used as third-line therapy because of adverse events or reduced efficacy as compared with newer agents.
- **Carbachol, dipivefrin**, topical cholinesterase inhibitors, and oral CAIs (eg, **acetazolamide)** are used as last-resort options after the failure of less toxic combinations.
- **Netarsudil** is the first approved Rho kinase inhibitor with efficacy similar to β-blockers. It may be used in combination therapy.
- Consider surgical procedures such as laser trabeculoplasty or surgical trabeculectomy when drug therapy fails, is not tolerated, or is excessively complicated. Antiproliferative agents such as **fluorouracil** and **mitomycin C** are used in glaucoma-filtering surgery to improve success rates by reducing fibroblast proliferation and consequent scarring.

Figure 64-1

Algorithm for the pharmacotherapy of open-angle glaucoma. [a]Fourth-line agents are not commonly used any longer or are commercially unavailable. [b]Most clinicians believe the laser procedure should be performed earlier (eg, after three-drug maximum, poorly adherent patient). (CAI, carbonic anhydrase inhibitor.)

TABLE 64-2

Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic	Dosage Form	Strength (%)	Usual	Mechanism of Action

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	Properties			Dose[a]	
β-Adrenergic Blocking Agents					
Betaxolol	Relative β_1 selective	Solution	0.5	One drop twice a day	All reduce aqueous production of ciliary body
		Suspension	0.25	One drop twice a day	
Carteolol	Nonselective, intrinsic sympathomimetic activity	Solution	1	One drop twice a day	
Levobunolol	Nonselective	Solution	0.25, 0.5	One drop twice a day	
Metipranolol	Nonselective	Solution	0.3	One drop twice a day	
Timolol	Nonselective	Solution	0.25, 0.5	One drop every day—one to two times a day	
		Gelling solution	0.25, 0.5	One drop every day[a]	
Adrenergic Agonists					
α_2-Adrenergic Agonists					
Apraclonidine	Specific α_2-agonists	Solution	0.5, 1	One drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow; only brimonidine has primary indication
Brimonidine		Solution	0.2, 0.15, 0.1	One drop two to three times a day	
Cholinergic Agonists, Direct Acting					
Carbachol	Direct and indirect acting	Solution	1.5, 3	One drop two to three times a day[a]	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Direct acting	Solution	1, 2, 4	One drop two to three times a day[a]	

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				One drop four times a day	
Cholinesterase Inhibitors					
Echothiophate	Indirect-acting cholinesterase inhibitor	Solution	0.125	Once or twice a day	
Carbonic Anhydrase Inhibitors					
Topical					
Brinzolamide	Carbonic anhydrase type II inhibition	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide		Solution	2	Two to three times a day	
Systemic					
Acetazolamide		Tablet	125 mg, 250 mg	125–250 mg two to four times a day	
		Injection (500 mg/vial)	250–500 mg		
		Capsule	500 mg	500 mg twice a day	
Methazolamide		Tablet	25 mg, 50 mg	25–50 mg two to three times a day	
Prostaglandin Analogs					
Latanoprost	Prostanoid agonist	Solution	0.005	One drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Latanoprostene bunod	Prostanoid agonist	Solution	0.024	One drop every night	Nitric oxide may also increase conventional outflow
Bimatoprost	Prostamide agonist	Solution	0.01, 0.03	One drop every night	
		Intracameral biodegradable implant	10 mcg	One implant per eye for the life of	

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				the patient	
Travoprost	Prostanoid agonist	Solution	0.004	One drop every night	
		Intracameral nonbiodegradable implant	75 mcg	One implant per eye for the life of the patient	
Tafluprost	Prostanoid agonist	Preservative free solution	0.0015	One drop every night	
Omidenepag isopropyl ophthalmic solution	E2(EP2) receptor agonist	Solution	0.002%	One drop every night	Penetrates the cornea, transforming into nonprostaglandin selective EP2 agonist active metabolite
Rho Kinase Inhibitors					
Netarsudil	Rho kinase inhibitor	Solution	0.02	One drop every night	Increases uveoscleral outflow, also decreases episcleral venous pressure
Combinations					
Timolol–dorzolamide		Solution	Timolol 0.5/dorzolamide 2	One drop twice daily	
Timolol–brimonidine		Solution	Timolol 0.5/brimonidine 0.2	One drop twice daily	
Brinzolamide–brimonidine		Suspension	Brinzolamide 1/brimonidine 0.2	One drop three times daily	
Netarsudil–latanoprost		Solution	Netarsudil 0.02/latanoprost 0.005	One drop every night	
Hyperosmotic Agents					All creates osmotic gradient and dehydrate vitreous
Mannitol		0.5-2.0 g/kg body weight	20		
Glycerol		1–1.5 g/kg body weight	50		

[a]Use of nasolacrimal occlusion will increase the number of patients successfully treated with longer dosage intervals.

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TREATMENT OF CLOSED-ANGLE GLAUCOMA

- Acute angle-closure crisis with high IOP requires rapid reduction in IOP. Iridectomy is the definitive treatment producing a hole in the iris that permits aqueous humor flow to move directly from the posterior to the anterior chamber.
- Drug therapy of an acute attack typically consists of a miotic (eg, pilocarpine), secretory inhibitor (eg, β-blocker, α_2-agonist, or CAI), or prostaglandin agonist.
- Osmotic agents are used to rapidly decrease IOP. Examples include oral **glycerin,** 1–2 g/kg, and **mannitol,** 1–2 g/kg IV.
- Topical corticosteroids can be used to reduce ocular inflammation and synechiae.

EVALUATION OF THERAPEUTIC OUTCOMES

- Successful outcomes require identifying an effective, well-tolerated regimen; closely monitoring therapy; and patient adherence. Many drugs or combinations may need to be tried before the optimal regimen is identified.
- Monitoring therapy for POAG should be individualized. Assess IOP response every 4–6 weeks initially, every 3–4 months after IOPs become acceptable, and more frequently if therapy is changed. Visual field and disc changes are monitored every 6–12 months, unless glaucoma is unstable or worsening.
- There is no specific target IOP because the correlation between IOP and optic nerve damage is poor. Typically, a reduction of 25%–30% is desired.
- The target IOP also depends on disease severity and is generally less than 21 mm Hg (2.8 kPa). Targets as low as less than 10 mm Hg (1.3 kPa) are desired for very advanced disease, continued damage at higher IOPs, normal-tension glaucoma, and pretreatment pressures in the low to middle teens.
- Monitor medication adherence because it is commonly inadequate and a cause of therapy failure.

See Chapter 119, Glaucoma, authored by Richard G. Fiscella, Ohoud A. Owaidhah, and Deepak P. Edward, for a more detailed discussion of this topic.

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